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Phase II trial of a 2-h infusion of gemcitabine plus carboplatin as first-line chemotherapy for advanced non-small-cell lung cancer

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Abstract *Purpose*: To evaluate the efficacy and safety of the combination of using gemcitabine as a rate infusion of 10 mg/m^2 per min with carboplatin in front-line chemonaive patients with advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: Fifty-four chemonaive patients with stage IIIB or IV NSCLC have been included, 44 males and 10 females, with a median age 63 years (range 19–75). Thirty-two (59%) patients had adenocarcinoma, 13 (24%) squamous cell, 1 (2%) large cell carcinoma and 8 (15%) others. Eight (15%) had stage IIIB and 46 (85%) stage IV. Treatment was consisted of 1,200 mg/m^2 gemcitabine given as a 2-h continuous infusion (10 mg/m^2 per min) on days 1 and 8 of each cycle an AUC 5 carboplatin as on day 1, repeating each cycle for every 21 days. A total of 223 chemotherapy cycles were administered, with a median of four cycles per patient (range 1–6), and 15 (28%) patients received all six cycles. *Results*: Of the 54 patients enrolled, all were evaluated for toxicity and 51 assessed for response. The overall response rate was 41% (95% confidence interval, 28–57%) with complete and partial responses of 4 and 37%, respectively. The median time to disease progression was 5.0 months (95% CI, 3.7–6.3 months), and median overall survival time was 11.5 months (95% CI, 9.9–13.1 months). One-year survival was 42%. The main grade 3–4 toxicity (according to the WHO scale) consisted of neutropenia (56%) and thrombocytopenia (57%). Patients were required platelet transfusion in 27 cycles (12%) and hematopoietic growth factors support care in 56 (25%) cycles. No bleeding episodes were recorded. Grade 3 nausea/vomiting occurred in 6% and grade 1–2 skin rash occurred in 43%. *Conclusions*: Prolonged gemcitabine infusion combined with carboplatin is manageable and tolerated, and its efficacy is similar to that of other chemotherapeutic schemes used for NSCLC treatment.

Keywords Non-small-cell lung cancer · Chemotherapy · Fixed infusion · Gemcitabine · Carboplatin

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Introduction

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in the world [1]. Platinum-based chemotherapy is considered as the standard treatment for advanced disease, with cisplatin considered the most effective for NSCLC [2]. The third generation agents, such as taxanes and vinorelbine, administered with a platinum derivative, have resulted in improved median and 1-year survival times when compared with either cisplatin alone or older platinum-based combinations in randomized trials [3–6].

Gemcitabine (2′,2′-difluorodeoxycytidine, dFdC), an analog of cytosine arabinoside (Ara-C), is a pyrimidine antimetabolite. It has consistently demonstrated a favorable toxicity profile and activity in advanced NSCLC, and its novel mechanism of action has encouraged its use in combination with traditional agents, such as cisplatin. Gemcitabine–cisplatin chemotherapy is considered as one of the most active regimens for advanced NSCLC, with an overall response rate (ORR) of 22–38% and median survival of 8.1–9.8 months in phase III trials [7–9]. Although several phase III trials of new platinum-based doublets [9–11] have produced similar results, a recent meta-analysis showed an absolute 1-year survival benefit of 3.9% for gemcitabine–cisplatin chemotherapy when compared to other platinum-containing regimens [12]. Gemcitabine requires phosphorylation intracellularly to its active form gemcitabine triphosphate. The phosphorylated forms of gemcitabine are retained within

the cells for longer periods, with an intracellular half-life of greater than 10 h for gemcitabine triphosphate. Preclinical studies have shown that the rate-limiting step in the activation of gemcitabine is the phosphorylation of gemcitabine by deoxycytidine kinase [13, 14]. The optimal rate of intracellular gemcitabine phosphorylation is reached with a plasma gemcitabine concentration between 10 and 20 μmol/L. This concentration corresponds to the saturation of deoxycytidine kinase activity within the cell [13, 15]. The continuous saturation of deoxycytidine kinase activity is achieved when gemcitabine is infused at a fixed dose rate (FDR) of 10 mg/m^2 per min [15–18]. The infusion of gemcitabine at 10 mg/m^2 per min has demonstrated increased tumor efficacy in a randomized phase II study of advanced pancreatic cancer [19]. A higher median intracellular gemcitabine triphosphate level was achieved in the FDR schedule. Infusion of gemcitabine at an FDR generally results in higher toxicity than that of a 30-min infusion. Increased myelosuppression and hepatic dysfunction are the usual toxicities observed [20, 21]. It has been reported that the phase II studies of standard doses of gemcitabine administered at 10 mg/m^2 per min in combination with platinum in patients with advanced-stage NSCLC [22].

Carboplatin shares a common mechanism of action with cisplatin, but has different pharmacokinetics and dose-limiting toxicities [23]. In contrast to cisplatin, standard doses of carboplatin (up to 400 mg/m^2) cause less nonhematological toxicities, and it can be administered in an outpatient setting. Carboplatin is an attractive alternative to cisplatin for combination with gemcitabine. The combination of gemcitabine and carboplatin has been explored in the treatment of patients with advanced NSCLC in the phase I and II trials, using 3 week as well as 4 week schedules [24–30]. The combination was feasible and active with response rates of up to 50%; however, day 21 schedule with gemcitabine administered on days 1 and 8 and carboplatin on day 1 were considered more appropriate due to less toxicity and better tolerability.

On the basis of the possible advantages of an FDR of gemcitabine, we designed a phase II trial to evaluate the response rate and tolerability of a 2-h infusion of gemcitabine (given at a constant dose rate of 10 mg/m^2 per min) plus carboplatin as first-line chemotherapy for advanced NSCLC. Secondary end points were time to progressive disease (TTP) and overall survival (OS).

Patients and methods

Patient selection

Chemonaive patients with histologically or cytologically confirmed locally advanced or metastatic stage IIIB or IV NSCLC not amenable to surgery or radiotherapy with curative intent were eligible for this study. Other eligibility criteria included the presence of at least one measurable lesion; age ≥18 to ≤75 years; Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤2, life expectancy ≥12 weeks; adequate bone marrow reserve (absolute neutrophil count $\geq 2.0\times10^9$ per L, platelet count $\geq 100\times10^9$ per L). Patients with asymptomatic brain metastases were eligible. No prior chemotherapy, immunotherapy or concomitant radiotherapy were allowed. Prior radiotherapy was acceptable if completed 4 weeks before the study entry.

Exclusion criteria included inadequate liver function [bilirubin >1.5 times above the normal range, aspartate transaminase (AST) and alanine transaminase (ALT) >3 times the normal range, or five times greater than the normal range in the presence of liver metastases]; severe alteration of renal functionality [serum creatinine >2 times the upper limit of normal (ULN)]; no second malignancies (except for carcinoma of the cervix uteri in situ and squamous cell carcinoma of the skin); peripheral neuropathy; untreated superior vena cava syndrome; hypercalcemia requiring intravenous (i.v.) treatment; and the presence of uncontrolled cardiac disease, uncontrolled diabetes mellitus, infections or other medical conditions that could have interfered with the trial.

Written informed consent was obtained from each patient before entering the study. The study was approved by the Ethics Committee of our center and was conducted in accordance with ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual.

Treatment plan and dose adjustments

Gemcitabine (Gemzar, Eli Lilly and Company, Indianapolis, IN, USA) 1,200 mg/m^2 was administered as a 120-min i.v. infusion on days 1 and 8 of a 21-day cycle. Carboplatin AUC = 5 was administered as a 4-h i.v. infusion on day 1, following gemcitabine. Carboplatin dosage calculation was based on the glomerular filtration rate according to the Calvert formula [31]. All patients were scheduled to receive at least two cycles of therapy, and up to six cycles if there was no evidence of disease progression. Treatment was stopped early in cases of patient refusal, severe toxicity, documented progressive disease (PD) or pregnancy. Patients with PD after two or four cycles or with stable disease after four cycles of chemotherapy were withdrawn from the study. Full supportive therapy, corticosteroids, anticonvulsants and antibiotics were given as needed. Antiemetic premedication included 5-HT$_3$ antagonists. No routine use of hematopoietic growth factors was planned. No prophylactic antibiotics were used. All patients were treated on an inpatient basis.

Dose adjustments during the treatment were based on hematological and nonhematological toxicities. On day 1, if neutrophil count was $<1.5\times10^9$ per L and/or platelet count was $<100\times10^9$ per L, chemotherapy doses were delayed (for up to 2 weeks) and doses were reduced by 25% to allow recovery from hematological toxicity.

On day 8, for a neutrophil count $<1.0\times10^9$ per L and/or platelets $<75\times10^9$ per L, the gemcitabine dose was omitted, and the cycle continued with one gemcitabine dose not given. Patients not recovering from hematological toxicity (neutrophil count $>1.0\times10^9$ per L and platelets $>75\times10^9$ per L) within 2 weeks were withdrawn from the trial. Doses were reduced by 25% for any grade 3 nonhematological toxicity (excluding nausea, vomiting and alopecia). Treatment was discontinued in the event of grade 4 or frequent grade 3 nonhematological toxicity. For grade 2–4 neurological toxicity, carboplatin treatment was delayed until the patient recovered to grade 1; then the dose was reduced by 25%. If no recovery to grade 1 was achieved within 3 weeks, the patient was discontinued from the trial.

Baseline and treatment assessments

Pretreatment evaluation included the physical examination; ECOG-PS; chest X-ray; brain, thoracic and abdominal computer tomography scan (CT scan); bronchoscopy (if not performed at the time of diagnosis); bone scan; electrocardiogram; complete blood count and blood chemistry with liver function tests and creatinine clearance. On days 1 and 8, a physical exam (including weight) was performed, and ECOG-PS and blood count were assessed. All measurable and evaluable lesions were assessed by the same method used at baseline. Response to therapy was assessed for every two cycles with clinical and/or radiological tumor assessment. Patients who finished six cycles of chemotherapy were assessed every 2 months.

In responding patients, a confirmatory assessment was repeated after at least 4 weeks, according to the response evaluation criteria in solid tumors (RECIST) [32]. Assessment of TTP was determined by measuring the time interval from the beginning of treatment until the first documentation of progression regardless of the patient's treatment status. OS was determined by measuring the time interval from the beginning of the treatment to the date of death or last contact. Toxicity was evaluated according to the WHO criteria. No quality of life questionnaire was used in the present study.

Statistical analysis

A two-stage design was used for the study. Using the Simon hypothesis, assuming a response rate of 40%, a probability of error of 5% and a power of 90%, a total of 54 patients were to be enrolled, with at least five responses to be noted in the first 19 patients. Treatment was considered as effective if at least 16 objective responses were observed. Every patient included in the study was considered evaluable [intent-to-treat (ITT) analysis]. Response rates, including 95% confidence intervals (CIs), were calculated on an ITT basis. Time-to-event end points were calculated using the Kaplan–Meier method with the appropriate censoring [33]. All analyses were performed using SPSS for Windows 11.5.

Results

Patient characteristics

From November 2002 to March 2005, a total of 54 patients were enrolled in this trial in our center. Patients' characteristics at baseline are listed in Table 1. The majority of patients were males (81%), with a median age of 63 years (range 19–75). Performance status was 0 in 13%, 1 in 54% and 2 in 33% of patients; 46 (85%) patients had stage IV and 8 (15%) had stage IIIB disease. Histology was predominantly adenocarcinoma (59% of the patients).

All patients were assessable for the safety analysis and 51 patients were assessable for response. Three patients were excluded from the response analysis because they did not complete three cycles of chemotherapy and did not show early progression; all three patients refused continuation of treatment because of personal aspects after the first cycle.

Efficacy

Of the 51 eligible patients, the ORR was 41% (95% CI, 28–57%), including two complete responses (CRs, 4%) and 19 partial responses (PRs, 37%). As per the ITT analysis, the ORR was 39%. With a median follow-up time of 10.8 months, by the closeout date, 8 patients (16%) were alive without progression and 43 patients

Table 1 Baseline patient's characteristics

	No. of patients	%
No. included	54	–
Median age (years)	63 (19–75)	–
Male/female	44/10	81/19
<65 years	28	52
≥65 years	26	48
ECOG performance status		
0	7	13
1	29	54
2	18	33
Stage		
IIIB	8	15
IV	46	85
Histology		
Squamous	13	24
Adenocarcinoma	32	59
Large cell	1	2
Others	8	15
Sites of metastases		
Lung	26	48
Liver	6	11
Bone	17	31
Nodes	12	22
Other	9	17
No. of metastasis sites		
1	30	56
2	15	28
3	3	6
≥4	1	2

(84%) had progressed. As at the closeout date, 15 (29%) patients were still alive and 36 (71%) patients had died. The median TTP was 5.0 months (95% CI, 3.7–6.3 months), median OS time was 11.5 months (95% CI, 9.9–13.1 months) and 1-year survival was 42%(95% CI, 26–57%) and 2-year survival was 19% (95% CI, 4.4–34%) (Figs. 1, 2).

A total of 223 chemotherapy cycles were administered, with a median of four cycles per patient (range 1–6), and 3 (6%) patients received one cycle, 19 (35%) three cycles, 12 (22%) four cycles, 5 (9%) five cycles and 15 (28%) patients received all six cycles. The planned dose intensity was 800 mg/m^2 per week for gemcitabine and 1.67 AUC/week for carboplatin. Dose intensity for all 54 patients was 762 mg/m^2 per week for gemcitabine and 1.54 AUC/week for carboplatin, with 95% of the planned gemcitabine dose and 92% of the planned carboplatin dose delivered.

Toxicity

The main hematological toxicities (Table 2) were transient grade 3–4 neutropenia observed in 30 (56%) patients, grade 3–4 thrombocytopenia observed in 31 (57%) and grade 3–4 anemia in 16 (30%) patients. Patients required platelet transfusion in 27 cycles (12%), and hematopoietic growth factors support care in 56 (25%) cycles. No bleeding episodes were recorded. Non-hematological toxicity was generally mild (Table 3). Grade 3 nausea/vomiting occurred in 3 (6%) patients. Grade 1–2 skin occurred in 23 (43%) patients. No serious adverse events were reported during the study and none of the patients died from the toxicity.

Although the protocol specified 21 days between cycles, 176 cycles (79%) received all treatment cycles within the protocol 21-day period. Twenty-six cycles (12%) were delayed for fewer than 7 days; seven cycles (3%) were delayed for more than 7 days. Of these, 30 cycles (14%) were delayed for toxicity reasons.

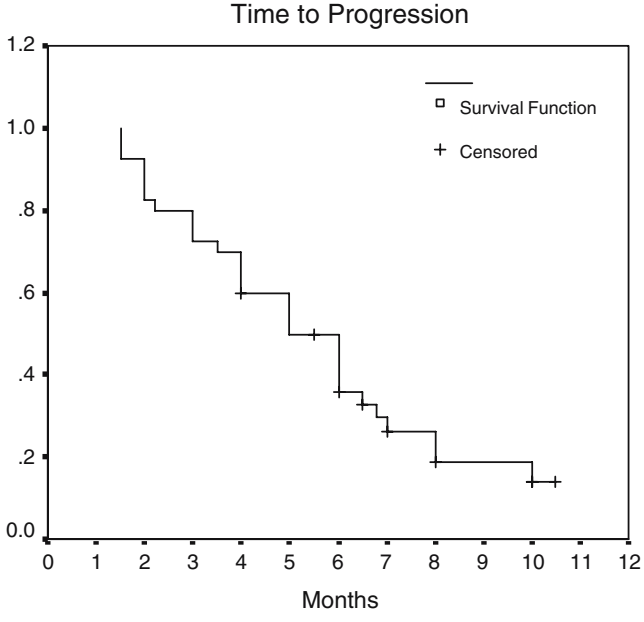

Fig. 1 Kaplan–Meier curve for time to progression

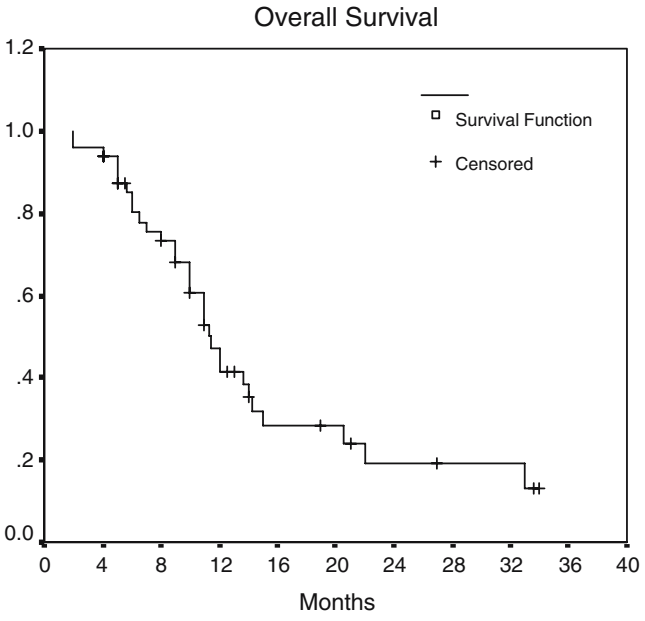

Fig. 2 Kaplan–Meier curve for overall survival

Discussion

The combination of gemcitabine and carboplatin as a front-line regimen for advanced NSCLC may be an appealing choice, allows cisplatin to be avoided, and,

Table 2 Hematological toxicities

Grade	Assessable patients ($n=54$)				Assessable cycles ($n=223$)			
	1	2	3	4	1	2	3	4
Leucocytopenia	5 (9%)	19 (37%)	19 (35%)	3 (5.6%)	38 (17%)	68 (31%)	46 (21%)	3 (1%)
Neutropenia	2 (4%)	9 (17%)	17 (32%)	13 (24%)	24 (11%)	35 (16%)	32 (14%)	21 (9%)
Febrile neutropenia	1 (2%)	0	2 (4%)	0	4 (2%)	0	2 (1%)	0
Anemia	9 (17%)	13 (26%)	10 (19%)	6 (11%)	46 (21%)	38 (17%)	26 (12%)	9 (4%)
Thrombocytopenia	6 (11%)	4 (7%)	11 (20%)	20 (37%)	21 (9%)	22 (10%)	31 (14%)	34 (15%)
Bleeding	0	0	0	0	0	0	0	0

Table 3 Nonhematological toxicities

Grade	Assessable patients ($n = 54$)				Assessable cycles ($n = 223$)			
	1	2	3	4	1	2	3	4
Nausea/vomiting	26 (48%)	9 (17%)	3 (6%)	0	71 (32%)	22 (10%)	3 (1%)	0
Skin	11 (20%)	12 (22%)	0	0	22 (10%)	15 (7%)	0	0
Diarrhea	1 (2%)	0	0	0	1 (0.4%)	0	0	0
Constipation	6 (11%)	1 (2%)	0	0	14 (6%)	2 (1%)	0	0
Increased AST	11 (20%)	3 (6%)	0	0	21 (9%)	4 (2%)	0	0
Increased creatinine	0	0	0	0	0	0	0	0
Alopecia	18 (33%)	13 (24%)	2 (4%)	0	85 (38%)	34 (15%)	5 (2%)	0
Neurological toxicity	1 (2%)	0	0	0	4 (2%)	0	0	0
Mucositis	3 (6%)	0	0	0	3 (1%)	0	0	0

therefore, it can be given to patients with an impaired renal function in the elderly. Furthermore, it is likely to present an acceptable toxicity profile. Our study confirmed the activity and manageable toxicity profile of 2-h infusion of gemcitabine plus carboplatin in patients with stage IIIB/IV NSCLC. We observed an ORR of 41%, with 2 CRs and 19 PRs. Median TTP was 5.0 months (95% CI, 3.7–6.3 months) and median OS was 11.5 months (95% CI, 9.9–13.1 months).

Two phase III randomized trials have evaluated the activity and toxicity of gemcitabine–carboplatin in NSCLC patients [34, 35]. The large difference between these two trials and our trial was gemcitabine administered suing an FDR of 10 mg/m^2 per min, although the dosage of gemcitabine and carboplatin in these two trials was same as our study. Gemcitabine–carboplatin (GC regimen) were a 3-week schedule, gemcitabine 1,200 mg/m^2 intravenously (i.v.) over 30 min on days 1 and 8, carboplatin AUC = 5 i.v. on day 1 in these two phase III randomized trials. Both trials included chemonaive patients, and response rates were 29 and 42%, respectively. TTP was 4.8 months and OS was 8.0 months in the Zatloukal trial. In the study conducted by Rudd et al., PFS was 5.3 months and median survival was 10.0 months. These results were similar to those observed in our trial, but the different characteristics of our cohort included a larger percentage of stage IV disease (85% in our study vs. 59% in the Zatloukal trial and 55% in Rudd trial), and a lower percentage of patients with a performance status 0–1 (67% in our study vs. 88% in Rudd trial).

In our investigation, carboplatin was administered on day 1, and gemcitabine was administered on days 1 and 8 at a constant dose rate of 10 mg/m^2 per min for 2 h. Nonetheless, the most outstanding feature of our schedule as compared to the previous studies was prolonged gemcitabine infusion. Gemcitabine has provided a small but significant clinical benefit in advanced NSCLC, when administered at a dose of 1,000 mg/m^2 given over 30 min on a weekly basis. Higher doses could improve clinical results, but pharmacological studies suggest that the augmentation of the dose when administered over a 30-min period does not increase either cytotoxicity or the therapeutic index [16, 17]. This is likely due to pharmacological features of gemcitabine, which is activated through several biochemical steps, with a key role for the enzyme deoxycytidine kinase, and it is rapidly saturated. Thus, increased doses would not be efficient, while longer infusion times would provide increased intracellular concentrations, thus enhancing the agent's efficacy. As we learn more about the pharmacodynamics of gemcitabine, its optimal dose and scheduling when combined with carboplatin are still to be assessed.

In a randomized phase II study in patients with pancreatic carcinoma, patients were randomized to receive either gemcitabine at a dose of 2,200 mg/m^2 over 30 min or gemcitabine at a dose of 1,500 mg/m^2 over 150 min, with the drug given weekly for 3 weeks, every 28 days. Results suggest that a longer median survival with the infusion given at an FDR of 10 mg/m^2 per min compared to that of the standard 30-min infusion administered weekly [19]. Given these results in the pancreas, we may be able to successfully apply this FDR infusion schedule of gemcitabine to other tumors or in combination therapy.

A phase I study has demonstrated the tolerability of escalating doses of gemcitabine (600–900 mg/m^2) combined with AUC 5 carboplatin given over a 21-day schedule [36]. A phase II study of gemcitabine administered at 10 mg/m^2 per min combined with carboplatin has been conducted by Domine et al. in patients with advanced-stage NSCLC [37]. In this study, reported in the abstract form, gemcitabine 1,200 mg/m^2 was administered over 120 min on days 1 and 8 in combination with carboplatin AUC 5 day 1 for every 3 weeks. Response rate was 47%, median time to progression was 28 weeks and median survival 45 weeks.

The response rate observed with gemcitabine–carboplatin in the present trial was also comparable to the activity of prolonged gemcitabine infusion based combinations observed in the other phase II studies. Prolonged gemcitabine infusion has been evaluated in combination with docetaxel [38], producing response rates of 26%, PFS of 4 months and OS of 7 months.

The toxicity profile in the present study can be considered relatively substantial. In our study, the rate of grade 3–4 neutropenia was as high as 56%, comparing with 30% of Zatloukal's study, 34% of Rudd's and 37% of

Domine's study. The rate of grade 3–4 thrombocytopenia was also up to 57% of patients in our study. Patients required platelet transfusion in 26 cycles (12%), hematopoietic growth factors support care in 56 (25%) cycles. No bleeding episodes were recorded. The manageable hematological toxicity kept the number of dose adjustments low and resulted in high dose intensity for two drugs. Dose intensity for all 54 patients was 762 mg/m^2 per week for gemcitabine and 1.54 AUC/week for carboplatin, with 95% of the planned gemcitabine dose and 92% of the planned carboplatin dose delivered. In contrast to Domine study, the median relative dose intensity was 75% for gemcitabine and 89% for carboplatin.

As far as nonhematological toxicity is concerned, similar to both Zatloukal trial and Rudd trial, the results of the studies coincide. Skin rash was present in 43% of the patients in our study. Gastrointestinal toxicity was low, and increased AST and grade 3 alopecia were found in 26 and 4% of patients, respectively.

At present, the potential role of prolonged gemcitabine infusion may be yet tested in future studies in an attempt to determine the most appropriate combination and its potential superiority over rapid infusion. However, our findings do not suggest that carboplatin combined with prolonged gemcitabine infusion provides an advantage over conventional schemes involving rapid infusion, but the characteristics in our study presented a larger percentage of stage IV disease and a lower percentage of patients with a performance status 0–1.

In conclusion, the present investigation showed that the antitumor activity and manageable toxicity profile of carboplatin combined with prolonged gemcitabine infusion confirm it as an attractive option for advanced NSCLC treatment. The manageable toxicity profile of this regimen also justifies its use in patients in whom cisplatin may not be feasible, such as the elderly or unfit. In the era of targeted therapies, this combination deserves to be studied further in association with new agents, such as the antivascular endothelial growth factor bevacizumab, or the monoclonal antibody antiepidermal growth factor receptor cetuximab.

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